Malignancy After Renal Transplantation: A Review

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INTRODUCTION

Renal transplantation provides a significant mortality benefit to patients with End-Stage Kidney Disease (ESKD) compared to those remaining on renal replacement therapy (RRT), with many centers reporting one-year graft survival rates of 95%.[1] The increase in allograft "half-life" is seen with both living donor kidney transplants (LDKT) and deceased donor kidney transplants (DDKT), and correlate to advances in immunosuppression options.[2] As kidney transplant recipients are living longer, careful monitoring for associated complications such as post-transplant malignancy is necessary. Post-transplant malignancy is the third most common cause of death in renal transplant recipients, with some malignancies occurring at much higher rates compared to the general population.[3] Immunosuppressant medication as well as oncogenic viruses seem to play a major role in malignancy development. This review will discuss malignancy after renal transplantation and offer an approach to caring for these patients.

EPIDEMIOLOGY

When to Suspect Malignancy

Renal transplant recipients have at least a 3- to 5-fold increase in malignancy incidence compared to the general population. This increased risk is much more significant for specific malignancies such as non-melanoma skin cancer (NMSC), while some other more common cancers such as prostate and lung cancers occur at approximately the same rate in transplant patients.[1,3] Several donor and recipient factors play an important role in malignancy development. ESKD itself appears to be oncogenic for the development of renal malignancy, with standardized incidence ratios (SIR) of 1.42 compared to age-matched cohorts without ESKD.[4] This is attributed to the development of acquired cystic kidney disease in this patient population, which markedly increases the risk of developing malignancy in these senescent organs.[5] Time spent on dialysis before transplantation has also been identified as a risk factor for developing post-transplant malignancy. Pre-transplant malignancy in either the donor or recipient, as well as susceptibility to various oncogenic viruses also contribute this risk. Differences in the donor type of transplant are associated with varying malignancy risk. Recipients of living-donor kidneys are at lower risk of cancer overall, particularly for genitourinary cancer and post-transplant lymphoproliferative disorder (PTLD).[6]

Undoubtedly the most important factor in post-transplant malignancy occurrence is prolonged exposure to immunosuppression – medications required to prevent the transplanted kidney from rejection. Immunosuppressants impair the body's immune surveillance of oncogenic mutations which would terminate such sequences under normal circumstances. Although improvements in immunosuppressive therapy has resulted in improvements in long-term graft survival, longer exposure is associated with a higher rate of de novo malignancy in transplant recipients.[1]

In the US, the risk of developing NMSC after renal transplantation is more than 20-fold higher than that of the general population. The other commonly encountered post-transplant malignancies are those influenced by oncogenic viruses (**Table 1**). Some of the more familiar malignancies in the general population such as breast, prostate, lung, uterine and pancreatic cancers tend to occur at about the same rate (or slightly less frequent) in kidney transplant recipients. Other more common malignancies such as colon, bladder and esophageal cancers occur at a rate approximately 2–5 times higher in transplant patients.[3]

Table 1. Viruses commonly associated with malignancy after renal transplantation. *Adapted from Morath C, Mueller M, Goldschmidt H, Schwenger V, Opelz G, Zeier M. Malignancy in renal transplantation. J Am Soc Nephrol. 2004;15(6):1582-8.*

Virus	Malignancy Type
Epstein-Barr Virus (EBV)	Post-Transplant Lymphoproliferative Disorder (PTLD)
Human Herpesvirus 8 (HHV-8)	Kaposi's Sarcoma
Human Papillomavirus (HPV)	Cervical Cancer Vulvar Cancer Penile Cancer Skin and Tonsillar Cancer
Hepatitus C Virus (HCV), Hepatitus B Virus (HBV)	Hepatocellular Carcinoma (HCC)

Transplant recipients should be monitored closely for the development of de novo malignancy throughout their entire post-transplant course, but as alluded to previously, malignancy risk increases with duration of follow-up. The risk of any malignancy after 10 years of renal transplantation is reported to be almost 14-fold higher than the general population, compared to much lower rates at 1- and 3-years post-transplant.

PATHOGENESIS

Immunosuppression Regimen/Host Factors/Viral Causes

Several factors contributing to post-transplant malignancy development have been identified including patient age, sun exposure, previous malignancy, concomitant viral infection, the type and intensity of immunosuppression and duration of dialysis pre-transplant. The effect of the intensity of immunosuppression on malignancy development is demonstrated across the various solid organ transplants and their post-transplant malignancy rates. Heart and lung transplant recipients require higher levels of immunosuppression than their kidney counterparts, and this is associated with a higher incidence of malignancy.[7] Immunosuppression intensity as an independent risk factor for post-transplant malignancy is also supported by studies comparing higher vs lower cyclosporine trough levels, with a 12% reduced incidence in the latter group.[8]

In the "modern era" of immunosuppression, anti-rejection regimens have been more customized to the individual recipient, based on the perceived risk for rejection. It is now recognized that the development of alloantibodies directed against the graft has a significant adverse impact on allograft survival and the previous practice of reducing the intensity of immunosuppression among transplant recipients of older vintage is no longer standardly applied. Although this practice may ultimately improve long-term allograft outcomes, there is an associated increase in malignancy incidence attributed to heightened immunosuppression exposure.

The type of immunosuppression used may also influence the risk of malignancy in the post-transplant setting. Lim et al. demonstrated that the risk for malignancy after first kidney transplantation was significantly higher in patients treated with T cell–depleting antibodies for treatment of acute rejection compared with those recipients not experiencing acute rejection, with most confined to the genitourinary tract.[9] Similarly, T cell depletion using anti-thymocyte globulin as induction therapy has also been associated with higher rates of post-transplant lymphoproliferative disease (PTLD) compared to less intense regimens (e.g., anti-IL-2 receptor antibodies). Furthermore, calcineurin inhibitors (CNIs) such as tacrolimus and cyclosporine raise transforming growth factor (TGF-β) levels which may promote tumor growth.[1] However, not all immunosuppressants are considered oncogenic. Mammalian target of rapamycin (mTOR) inhibitors, including sirolimus and everolimus, may have anti-neoplastic properties and inhibit angiogenesis of tumor cells.[10] More information is needed to make more definitive conclusions regarding mTOR inhibitors and malignancy risk, as one meta-analysis suggests a decrease in NMSC but an increased risk in prostate cancer.[11]

Immunosuppression itself impairs the host's ability to survey the immune system for potentially hazardous mutations. This is perhaps best demonstrated in the higher incidence of post-transplant skin cancers (specifically NMSC) and viral-related malignancies. It is well known that sun exposure predisposes the host to carcinogens, which can eventually lead to skin cancer. The immune system is responsible for identifying mutations associated with carcinogen exposure and terminating them prior to malignancy development. Without inhibitory checkpoints in place, malignancy develops at much higher rates. Several viruses are associated with malignancy in immunocompromised hosts (**Table 1**). The viruses encode oncogenic proteins to promote malignancy development.[12] In immunocompetent individuals the viruses do not cause significant illness and remain dormant. However, the virus activity is unopposed in immunosuppressed individuals, and malignancy may subsequently occur.

Donor factors such as the unknowing donation of neoplastic cells at the time of transplantation are possible, but more commonly, malignancy occurs de novo in the recipient. Host factors play an important role in this risk. For example, the incidence of renal cell carcinoma (RCC) in kidney transplant recipients is influenced by male sex, increasing age, African ancestry, acquired cystic kidney disease, and the longer duration on dialysis. The underlying etiology of ESKD can also play a role, as evidenced by the increased of RCC in patients with tuberous sclerosis. Glomerulonephritis (GN) accounts for approximately 10% of the ESKD population in developed countries. Many of these disease states require immunosuppression as part of the treatment regimen, some of which may be potentially oncogenic (e.g., cyclophosphamide). Exposure to such medications may double the risk of post-transplant malignancy compared to other allograft recipients and should therefore be well-documented in patient records.[14]

SKIN CANCERS

Skin cancers are by far the most common post-transplant malignancy, accounting for approximately 40% of cases.[2] Patients with fair complexion are at greatest risk, and rates increase with prolonged sun exposure and geographic location. In Australia, for example, the cumulative risk of skin cancer post-transplant is as high as 45% at 11 years and 70% at 20 years.[3] The risk of melanoma is 3–4 times higher in renal transplant recipients, but the non-melanoma skin cancers (NMSC) are far more common. These NMSC include

basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and Kaposi's sarcoma. Kasiske et al demonstrated that cumulative incidence of NMSC was 0.3%, 0.9%, 2.3%, 5.0%, and 7.4% at months 3, 6, 12, 24, and 36 months respectively.[15] BCC and SCC are responsible for > 90% of skin cancers post-transplant. Although NMSC is not considered as aggressive as some other malignancies, SCC in transplant patients carries a 3-year mortality rate of 46% for metastatic disease and recurrence is common.[16] Skin surveillance and ultraviolet (UV) protection is strongly recommended in the post-transplant period. CNIs such as tacrolimus and cyclosporine are highly associated with NMSC post-transplant and those experiencing recurrent skin cancers typically are frequently converted to alternative regimens such as mTOR inhibitors to mitigate this risk.[17] Once identified, the risk of skin cancer recurrence is high, and the clinician should emphasize the importance of skin surveillance and protection post-transplant.

Kaposi's sarcoma (KS) is an angioproliferative cutaneous cancer caused by human herpesvirus 8 (HHV-8) in immunocompromised hosts. They are purple-red-bluish lesions presenting as non-painful, non-pruritic, macules, papules or nodules. The incidence of KS is greatly increased in renal transplant recipients, particularly in certain ethnic groups occurring in up to 5% of transplant patients.[18] KS is more strongly associated with CNIs than other immunosuppressants. Visceral involvement of the GI tract or other mucosal surfaces is possible but less common, and outcomes are variable. Approximately one-third of patients achieve complete remission with altering immunosuppression therapy, but another one-third of patients die at 3 years after diagnosis.[3]

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE (PTLD)

PTLD includes several lymphoid disorders such as lymphomas (both Hodgkin and NHL), lymphoid leukemias and multiple myeloma. The World Health Organization (WHO) classifies PTLD into four categories: early lesions, polymorphic, monomorphic, and classical Hodgkin's lymphoma (cHL). PTLD has an incidence rate of 1.8% at 10-years post-transplant and is more common in pediatric transplant recipients. It is typically associated with Epstein-Barr Virus (EBV) infection, which chronically infects B-cells and leads to their proliferation. Immunosuppression inhibits T-cell regulation of the EBV-infected B cells, and uncontrolled proliferation may ensue.[19] The risk of PTLD is highest when an EBV (–) patient receives a kidney from an EBV (+) donor.

Although PTLD can occur at any time post-transplant, Non-Hodgkin Lymphoma tends to be the most aggressive and can occur within the first year after transplant when immunosuppression is highest and there is more risk for viral infection. More recent data suggests the interval to disease onset is increasing to later in the post-transplant course at 48–81 months.[20] The lymphoid proliferations can be localized to lymph nodes or disseminated (extra-nodal) to involve the transplanted organ, or other native organs such as the central nervous system (CNS). In kidney transplant patients, the most common location for PTLD involves the gastrointestinal tract. Clinical presentation is highly variable and may include lymphadenopathy, night sweats, weight loss or chills. Treatment includes reduction of immunosuppression, and often a B-cell directed chemotherapy regimen. However, there is no consensus on how immunosuppression should be adjusted.

ANOGENITAL CANCERS

Anogenital malignant neoplasms occur with a 14- to 50-fold increased incidence in kidney transplant patients and human papilloma virus (HPV) infection plays a major role in the development of such cancers. These include cervical, vulvar, vaginal, penile and anal malignancies. [21] The incidence of HPV infections in kidney transplant recipients is 17% to 45%, with a low rate of cytologic alterations found on pap testing.[22,23] Vulvar and vaginal cancers are the least common gynecologic cancers in the general population. Like cervical cancer, most vulvar cancers after transplantation are HPV-related with the high-risk HPV types playing the major role in the pathogenesis. Among kidney transplant patients, a younger age at transplantation (18–34yo) is associated with increased risk of cervical cancer whereas vulvar cancer is more likely to occur at 5 or more years after transplantation.[24]

The choice, duration and intensity of immunosuppressive agents may influence the incidence of gynecological cancer development; however, studies on the direct effect of specific immunosuppressants on gynecologic cancers are sparse and conflicting. One hypothesis suggests immunosuppression may contribute to reactivation of latent HPV infections, including high-risk oncogenic HPV types.[25] A US study of 187,649 solid organ transplant recipients (64% renal transplant), did not report an increase in invasive cervical cancers after transplantation, although it noted an increase of in situ carcinoma; this may be explained by very close follow-up due to chronic immunosuppression and subsequent earlier detection of noninvasive cervical lesions. Decisions regarding whether to withdraw or reduce immunosuppression after a gynecologic cancer in the post-transplant population should be individualized.

OTHER CANCERS AND THOSE WITHOUT INCREASED RISK

Other malignancies after renal transplantation occur at varying rates. Some of the more commonly encountered cancers in the general population (breast, prostate, lung, pancreas and uterine) occur at about the same rates in renal transplant

Table 2. Standard Incidence Ratios (SIRs) of various malignancies after renal transplantation compared to the general population.

Standard Incidence Ratio (SIR)	> 20x	10–20x	2–5x	1–2x
Type of Cancer	NMSC Lip Cancer Oropharyngeal Kaposi Sarcoma	Cervical Vulvar Lymphoma Renal and Ureter Bladder Thyroid Neuroendocrine	Colorectal Melanoma	Prostate Lung Pancreas Breast Uterine

recipients. Colon cancer is encountered at a slightly higher rate in transplant patients, 2–5 times the general population. Finally, urologic malignancies including the bladder, ureters and kidneys occur at rates 5–20 times higher in renal transplant recipients.[15] **Table 2** contains a more comprehensive list of malignancies and their standardized incidence ratios (SIRs) after renal transplantation.

PREVENTION

Post-Transplant Cancer Screening Guidelines

Although the increased risk of malignancy after renal transplant is well established, there is little evidence to support screening guidelines in this complex patient population. [26] As one might expect, the guidelines are adopted from those used for the general population as well as for those cancers seemingly unique to renal transplant recipients. For malignancies already associated with cancer screening guidelines in the general population, many societies suggest utilizing the same approach in renal transplant recipients. This includes colon, breast, and prostate cancers. Lung cancer screening is recommended *against* by the American Society of Transplantation (AST) in renal transplant recipients, as is the case for renal and other urologic cancers despite their increased incidence in the transplant population.[27] Skin cancer screening with self-examination and annual dermatology surveillance for highest-risk transplant patients is recommended, and risk stratification tools exist to aid the clinician in identifying these individuals.[28] Despite these recommendations, evidence is lacking to support changes in outcomes.

Cervical cancer is the only gynecologic cancer for which there are effective screening tests for the general population to detect more treatable precancerous lesions. The American College of Obstetricians and Gynecologists and AST recommended more frequent, annual screening for cervical cancer in renal transplant recipients. Still some other societies recommend pap testing with pelvic examination every 3 years, which is in line with the general population guidelines.[29] Screening for PTLD/lymphomas are recommended against by most societies, and hepatocellular carcinoma (HCC) screening with abdominal ultrasound is only recommended in transplant patients with compensated cirrhosis.

A lack of supporting evidence is not the only limitation of cancer screening in renal transplant recipients. In the general population, those with a life expectancy of 5–10 years are typically excluded from the cancer screening guidelines. Mortality rates in renal transplant patients vary depending on age and comorbidities at time of transplantation, but it should be noted that mortality after diagnosis of malignancy is high in this population. In Australia and New Zealand, the 5-year survival rate for a transplant patient after malignancy diagnosis had been less than 10%.[27] Those with a malignancy history prior to transplant factor into the limitations as well. Depending on the type of malignancy, patients should be deemed cancer-free for 2–5 years prior to transplant consideration. However, with better survival outcomes after transplant compared to maintenance on replacement therapy (RRT), development of novel chemotherapeutic agents and more individualized immunosuppression, there has been discussion that the current recommendations may be too restrictive. Prospective data in the transplant population is needed to provide better guidance to the clinician regarding cancer screening.

MANAGEMENT

The cornerstone of post-transplant malignancy management is the reduction of immunosuppression. Management depends on the type and severity of malignancy and the benefits of decreasing immunosuppression to fight the cancer must be weighed against possible allograft rejection and/or failure. Targeting a lower immunosuppressant drug level is commonplace in the setting of malignancy, and clinicians may choose to transition from CNI to mTOR inhibitors (especially in the setting of skin cancers). There is some evidence to suggest mTOR inhibitors have anti-neoplastic properties and may be helpful in bridging the difficult gap between malignancy management and allograft protection, although this is not true of all cancers and more information is needed.

Another approach to the management of post-transplant malignancies is to withdraw entire classes of immunosuppression altogether. Although immunosuppression regimens are transplant center-dependent, the majority of programs are still using a three-drug regimen consisting of a CNI, anti-metabolite (mycophenolate mofetil or azathioprine), and prednisone.[2] In addition to changing the CNI to an mTOR inhibitor, the clinician may elect to discontinue the anti-metabolite medication to lower the overall immunosuppressive burden. This would seem more beneficial in those taking azathioprine, as it has been linked to neoplasia while mycophenolate mofetil may reduce the relative risk of some malignancies such as PTLD.[30]

Chemotherapy may be used depending on the type of

malignancy encountered. Perhaps the most challenging scenario is when faced with a malignancy which is typically responsive to immunotherapy. More recent breakthroughs in oncology have brought immunotherapy to the forefront of cancer treatment. Some of these therapies provide improved outcomes compared to the previous standard of care, and the immune checkpoint inhibitors have been the most successful types of immunotherapy to date. The clinical dilemma involves activation of T-cells to combat neoplastic cell growth. Activation of previously dormant T-cells (thanks to immunosuppression) can lead to allograft rejection due to recognition of donor antigen in the kidney.[31] An individualized approach to each transplant patient with malignancy is likely best to determine the best course of action.

SUMMARY

In the modern era of immunosuppression, we are seeing better outcomes in renal transplant recipients. As a result, the effects of prolonged exposure to immunosuppression, such as post-transplant malignancy, are more pronounced. A transplant recipient's previous medical and oncologic history, opportunistic viral exposures, and immunosuppression regimen should all be considered when managing or screening for post-transplant malignancy. Screening guidelines in transplant patients are often adopted from those of the general population, and more prospective evidence is needed for future guidance. Reduction in immunosuppression is a cornerstone of post-transplant malignancy management, and there is some evidence to suggest mTOR inhibitors and the anti-metabolite mycophenolate mofetil are less "oncogenic" compared to CNIs or azathioprine. Finally, all decisions to reduce immunosuppression and/or treat active malignancy must be weighed with the possibility of allograft rejection/failure and should be made in consultation with the patient's transplant team.

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